Outdoor Air Pollution and Lung Cancer

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In the 1950s evidence of an ongoing epidemic of lung cancer in the United States and Western Europe led researchers to examine the role of outdoor air pollution, which was considered by some to be a likely cause. Although epidemiologic research quickly identified the central role of cigarette smoking in this epidemic, and despite progress in reducing outdoor air pollution in Western industrialized countries, concerns that ambient air pollution is causing lung cancer have persisted to the present day. This concern is based on the fact that known carcinogens continue to be released into outdoor air from industrial sources, power plants, and motor vehicles, and on a body of epidemiologic research that provides some evidence for an association between outdoor air pollution and lung cancer. This article reviews the epidemiologic evidence for this association and discusses the limitations of current studies for estimating the lung cancer risk in the general population. It also identifies research needs and suggests possible approaches to addressing outstanding questions. *Key words*: air pollution, ambient air, epidemiology, fossil fuels, lung cancer, polycyclic aromatic hydrocarbons, review. — *Environ Health Perspect* 108(suppl 4):743–750 (2000). *http://ehpnet1.niehs.nih.gov/docs/2000/suppl-4/743-750cohen/abstract.html*

In the 1950s evidence of an ongoing epidemic of lung cancer in the United States and Western Europe led researchers to examine the role of outdoor air pollution, which was considered by some to be a likely cause. Although epidemiologic research quickly identified the central role of cigarette smoking in this epidemic (*1,2*), a body of epidemiologic research over the ensuing 40 years provides some evidence for an association between air pollution and lung cancer. This article reviews this evidence and discusses outstanding questions and research needs. Recent monographs and books provide more comprehensive reviews of the literature on air pollution from both indoor and outdoor sources and the occurrence of lung cancer (*3–5*).

Exposures to Carcinogens in Outdoor Air

Despite progress in reducing outdoor air pollution in Western industrialized countries, carcinogens continue to be released into outdoor air from industrial sources, power plants, and motor vehicles. Outdoor air, particularly in densely populated urban environments, contains a variety of known human carcinogens (Table 1). These substances are present as components of complex mixtures that may include carbon-based particles to which the organic compounds are adsorbed, oxidants such as ozone and sulfuric acid in aerosol form. The combustion of fossil fuels for power generation or transportation is the source of most of the organic and inorganic compounds, oxidants, and acids, and contributes heavily to particulate air pollution in most urban settings. The radionuclides are emitted as a result of the combustion of fossil fuels as well as from mining operations, and the asbestos fibers result from sources such as building materials and vehicular brake linings.

Unfortunately, there are few long-term trend data for outdoor levels of known carcinogenic products of fossil fuel combustion that could be used to estimate long-term exposures for epidemiologic purposes. Available data indicate that over the past 20–30 years improvements have been made in some indices of air quality. According to a report of the Council for Environmental Quality (*6*), levels of benzo[*a*]pyrene in urban air decreased 70% between 1970 and 1980. Daisey et al. (*7*) reported that levels of sulfates and particulate-associated organic matter declined by 30–40% between 1964 and 1983 in two industrialized New Jersey locations in the United States.

The U.S. Environmental Protection Agency (U.S. EPA) collects data on six pollutants for which the U.S. government has promulgated national air quality standards, the "criteria pollutants." Particulate matter with an aerodynamic diameter < 10 μm (PM_{10}) is the criteria pollutant of greatest current interest with respect to lung cancer because particles ≤ 10 μm can be inhaled into the lung and carry carcinogenic substances on their surfaces. Comprehensive monitoring of PM_{10} has only been in place since 1988; before 1988 the U.S. EPA monitored only total suspended particulates (TSP), which include particles too large to be inhaled into the lung. Decreases in TSP were observed over the 1970s and early 1980s, but little change has been noted since 1990. From 1988 to 1995 the average annual mean concentration of PM_{10} fell by 17% (*8*). The PM_{10} standard was augmented recently by a $PM_{2.5}$ standard, so there are few data on trends in this pollutant.

The data collected by the U.S. EPA on the criteria pollutants reflect, for the most part, outdoor air pollution over relatively large geographic areas. However, the exposure of human populations to carcinogens in outdoor air may be the result of proximity to more localized sources such as industrial facilities, small businesses (e.g., automotive body or chrome-plating shops), municipal facilities (e.g., waste incinerators), or areas with high vehicular traffic. For example, data collected by Cass and colleagues (*9*) in Los Angeles, California, indicate that elemental carbon levels, mostly derived from diesel exhaust, declined in five of seven areas in Los Angeles between 1958 and 1981 but increased in two areas undergoing rapid growth.

Under the Clean Air Act Amendments of 1990, the U.S. EPA is charged with evaluating the risks of 189 hazardous air pollutants, primarily carcinogens from point sources. The combustion of fossil fuels for transportation and power generation contributes to the presence of these many known or suspected carcinogens in outdoor air. Some of the potentially more significant pollutants in terms of exposure prevalence and/or lung carcinogenicity are discussed in the following sections:

Polycyclic Organic Matter

Polycyclic organic matter (POM) as defined by the U.S. EPA in the Federal Clean Air Act in 1971 comprises a large and varied class of chemical compounds, including polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs, which are known carcinogens and mutagens (*10*) and are found in both the particulate and gas phases of outdoor air. In addition to those compounds released directly into the environment by combustion processes, others are created from primary combustion products, such as those emitted by diesel engines, via chemical and photochemical

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Parts of this review appeared in earlier reviews by the author, specifically Cohen et al. (*4*) and Samet and Cohen (*5*).

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Table 1. Selected known carcinogens in urban and rural ambient air.

Substance	Urban air	Rural air
Inorganic particulates (ng/m^3)		
Arsenic	2–130	< 0.5–5
Asbestos	10–100	–
Chromium	5–120	< 1–10
Nickel	10–1000	< 10
Radionuclides (Ci/m^3)		
^{210}Pb	$1 \times 10^{-15} - 30 \times 10^{-15}$	$5.5 \times 10^{-15} - 10 \times 10^{-15}$
^{212}Pb	$0.1 \times 10^{-15} - 4 \times 10^{-15}$	$0.03 \times 10^{-15} - 0.06 \times 10^{-15}$
^{222}Rn	$20 \times 10^{-125} - 1{,}000 \times 10^{-12}$	$0.1 \times 10^{-12} - 20 \times 10^{-12}$
Gaseous and particulate organic species (ng/m^3)		
Benzene	5–90	–
Benzo[*a*]pyrene	1–50	–
Benzene-soluble organics	1,000–2,000	200–300

Adapted from IARC (*10*).

reactions in the outdoor environment (*11–13*). Neither the contribution of these latter, secondary compounds, to total outdoor levels of POM nor their relative mutagenicity and carcinogenicity are well understood.

Although the combustion of fossil fuels is a ubiquitous source of POM in the urban outdoor environment, it is not the only source of human exposure to POM, and for some individuals it may not be the predominant source. Other human exposure to POM comes from inhaling wood and tobacco smoke and from the diet (e.g., from the consumption of grilled meat). Unfortunately for the conduct of epidemiologic research, there are currently no validated markers of exposure to POM from specific sources, either in outdoor air or biologic material.

Urban air contains a mixture of polycyclic organic compounds, but certain specific constituents, such as benzo[*a*]pyrene, have been extensively studied and are known to be carcinogenic. Benzo[*a*]pyrene has been used frequently as a surrogate or marker for combustion source air pollution in epidemiologic studies and for risk assessment. The literature on cancer risk in relation to occupational and environmental exposure to PAHs has recently been reviewed by Boffetta et al. (*14*), who concluded that PAHs are associated with increased lung cancer risk in a variety of occupational settings and with increased lung cancer risk in urban populations. Mixtures of polycyclic compounds encountered in occupational settings, such as coke-oven workers in the steel industry and coal gasification workers (*15,16*), also are known to cause increased occurrence of lung cancer in exposed workers (*17*). The levels of POM encountered in the outdoor urban environment, however, are substantially less than those encountered in heavily exposed occupational settings.

Particles

Like POM, particulate air pollution is not a single entity but rather a chemically and physically diverse group of pollutants derived from sources as diverse as crustal dust and sea spray and from the combustion of diesel fuel (*18*). As such, it is not possible to address generically the carcinogenicity of particles. Largely because carbonaceous particles produced by the combustion of fossil fuels are in the respirable range (generally < 1.0 μm in diameter) and known human carcinogens such as PAHs are adsorbed to their surfaces, attention has focused on combustion-source particles in urban air as potential lung carcinogens. However, recent evidence from animal experiments showed that rats exposed to high levels of relatively pure carbon particles developed lung tumors at the same rate as rats exposed to diesel exhaust particles when each was compared to unexposed controls, suggesting that particles per se might, under some conditions, be carcinogenic. The relevance of these findings for humans is controversial (*19*).

The combustion of fossil fuels for power generation and transportation produces gaseous pollutants such as sulfur dioxide (SO_2) and oxides of nitrogen (NO_x) that are converted into fine particulate air pollution in the atmosphere. Epidemiologic studies provide no consistent evidence of increased lung cancer risk from occupational exposure to SO_2; however, the International Agency for Research on Cancer (IARC) has classified strong sulfuric acid aerosol as a known human carcinogen based on epidemiologic findings of increased lung and laryngeal cancer in heavily exposed occupational groups (*20*).

Diesel

Diesel exhaust is a ubiquitous component of urban outdoor air pollution throughout the world, although few studies have estimated its proportional contribution. In one of the few studies that estimated the proportional contribution of diesel exhaust to outdoor air pollution, Cass and Gray (*21*) estimated that diesel exhaust contributed 7% of the fine particulate (< 2 μm) in the Los Angeles air basin in 1982.

On the basis of evidence from animal experiments and epidemiologic studies of occupationally exposed groups, IARC considers diesel exhaust to be a probable human carcinogen (IARC classification 2A) (*22*), although the mechanism by which exposure to diesel exhaust might produce lung cancer in humans remains to be determined. The evidence for the carcinogenicity of diesel exhaust has recently been extensively reviewed (*19,23*).

1,3-Butadiene

1,3-Butadiene is a volatile organic compound employed since the 1930s in the production of synthetic rubber. It is also emitted in automotive exhaust and has been classified by IARC as a probable human carcinogen (2A) on the basis of results of animal inhalation experiments, which indicated increases in tumors at multiple sites, including the lung. Epidemiologic studies of occupationally exposed populations (rubber workers and butadiene monomer production workers) have consistently observed increases in hematopoietic cancers but not in cancers of the respiratory system (*20,24*).

Aldehydes

Various aldehydes classified as hazardous air pollutants by the U.S. EPA (e.g., formaldehyde, acetaldehyde) are present in urban ambient air largely due to the combustion of gasoline and diesel fuel (*24*). Formaldehyde has been classified by IARC as a probable human carcinogen (2A) (*25*), on the basis of evidence from animal experiments and epidemiologic studies in occupational groups of exposure-related excess nasal and nasopharyngeal cancer. There is no consistent evidence that occupational exposure to formaldehyde is associated with increased lung cancer risk (*25*). The combustion of alternative fuels, such as methanol and oxygenated fuels containing the additive methyl tertiary butyl ether, results in greater aldehyde emissions and contributes to increased ambient concentrations in locales where they are widely used (*24*).

Epidemiologic Evidence on Outdoor Air Pollution and Lung Cancer

Several lines of epidemiologic research provide evidence about the association of ambient air pollution with lung cancer occurrence in the general population: *a*) studies comparing lung cancer risk in migrants to areas having differing lung cancer risk from the native country; *b*) studies comparing cancer rates among urban and rural populations; *c*) studies of populations residing near specific point sources of air pollution; *d*) case–control and cohort studies of lung cancer occurrence in the general urban population; and *e*) studies comparing the relative frequency of biologic markers

of air pollution exposure and of air pollution exposure and genetic damage.

Migrant Studies and Urban–Rural Comparisons

Studies of migrants reviewed elsewhere (*26*) provide limited evidence in support of the hypothesis that air pollution is associated with lung cancer risk. Migrants from countries with higher rates of lung cancer and higher levels of air pollution to countries with lower air pollution levels tend to develop lung cancer at rates higher than those of the new country of residence, suggesting that prior exposure was a risk factor. However, incomplete control for the effects of smoking and occupational exposure may account for these findings.

The earliest studies of air pollution and lung cancer contrasted lung cancer rates of urban and rural populations. Most studies found overall excesses on the order of 30–40% in the urban areas and larger relative excesses among nonsmokers. The attribution of these results to differences in air quality was strengthened by evidence of urban–rural differences in ambient levels of carcinogens such as benzo[*a*]pyrene and by the frequent persistence of the urban–rural differences after adjustment for cigarette smoking. Doll and Peto (*27*), in their widely cited monograph, *The Causes of Cancer*, cast doubt on the causal role of air pollution because early research had not accounted for the effects of urban dwellers who started smoking at younger ages as cigarette smoking became increasingly prevalent in the early 20th century. However, Dean (*28*) controlled for the age at which smoking began and found that the urban–rural gradient persisted. Recent lung cancer incidence and mortality data continue to show evidence of urban–rural differences (*29,30*) and other studies document contemporary urban–rural gradients in the mutagenicity of airborne particulate matter across the United States (*31,32*). Nonetheless, the urban factor may reflect influences instead of, or in addition to, outdoor air pollution; these could include indoor air pollution, patterns of migration, occupational exposures, or factors related to population density.

Studies of Populations Residing Near Point Sources of Air Pollution

Residential proximity to industrial point sources of air pollution is a potential source of exposure to known or suspected carcinogens, as noted previously. Fossil fuel-fired (i.e., coal, oil, natural gas) electrical power plants emit known or suspected carcinogens (*12*), including metals such as chromium and nickel, radionuclides such as radon and uranium, and POM such as benzo[*a*]pyrene. Nonferrous metal smelters emit inorganic arsenic and other metals and SO_2 (*33*). Municipal solid waste incinerators emit heavy metals (e.g., lead), cadmium, PAHs, organic compounds (such as dioxins), and acidic gases (*34*). Unfortunately, these sources of air pollution are often located in or near poor working-class communities whose residents may, for a variety of reasons, be more susceptible to the effects of these pollutants (*35*).

In 1990, Pershagen (*36*) reviewed the available epidemiologic studies of lung cancer occurrence and residential proximity to industrial point sources of air pollution. Eleven studies estimated lung cancer risk associated with proximity to nonferrous metal smelters. Of these, five ecologic studies observed relative risks in males of between 1.2 and 2.0, but only one study accounted for employment at the smelter itself, and data on smoking were not available. These studies did not consistently observe elevations in risk among women. Six case–control studies presented conflicting results; several showed no association with residential proximity and did not account for either employment at the facility or smoking habits. Two studies that did account for these factors observed relative risks in males of 1.6 and 2.0. Ecologic studies of residential proximity to diverse industrial sources (e.g., petrochemical plants and steel mills) generally observed increased rates of lung cancer but were unable to control for confounders at the individual level, i.e., such factors as cigarette smoking and employment at the industrial facility itself.

Taking advantage of a "natural experiment" in which air pollution levels changed in a relatively rapid and clear-cut fashion over time, Archer (*37*) analyzed respiratory cancer mortality in two counties in Utah with very low smoking rates. The counties were similar in many respects, with low and nearly equal respiratory cancer mortality rates, until a steel mill constructed during World War II caused substantial increases in air pollution in one county. The subsequent differences in incidences of lung cancer cases were substantial within about 15 years after the increase in air pollution and have persisted. Presumably the prevalence of smoking remained constant, or at least equal, in the two counties. A third neighboring county, unaffected by pollution from the steel mill but with a population with higher smoking rates had higher lung cancer rates than either of the other two counties, underscoring the profound effects of cigarette smoking on lung cancer risk.

Elliott and colleagues (*38*) recently reported the results of an ecologic study of cancer incidence among 14 million people living near 72 municipal solid waste incinerators in Great Britain. Cancer rates and residential proximity to the incinerators were measured at the postal code level (which is roughly analogous to neighborhood); the relative risks (compared to national incidence rates) were adjusted for age, sex, geographic region, and an index of socioeconomic status. For several types of cancers (stomach, colorectal, liver, lung), excess relative risk was inversely related to distance of the residence from the incinerator. Lung cancer relative risks (95% confidence intervals [CIs]) were 1.08 (1.07, 1.09) and 1.06 (1.05, 1.07) for residences 0–3 km and 0–7.5 km, respectively, from the incinerator. However, Elliott and colleagues (*38*) also observed equal elevations in lung cancer risk in the areas proximal to the incinerators before construction of the facilities, leading them to conclude that residual confounding by unmeasured characteristics of the postal codes accounted for the apparent associations with proximity to the incinerators.

Ecologic studies, such as those of Archer (*37*) and Elliott et al. (*38*), have generally observed relative excesses of lung cancer in the more polluted areas of similar or slightly higher magnitude than the urban–rural studies (*5*). However, because incidence, exposure, and covariate data are all measured on the aggregate, or ecologic, level, it is difficult to account adequately for intraindividual and between-area differences in other risk factors (*39*).

Case–Control and Cohort Studies of Lung Cancer Occurrence in the General Urban Population

Cohort and case–control studies have the advantage of offering information on potential confounding and modifying factors such as cigarette smoking. Case–control studies provide an efficient approach to estimating the relative risk of lung cancer in relation to air pollution exposure without having to collect information on an entire cohort or study population. In the case–control design, cases of lung cancer that have occurred in the population are ascertained and classified according to exposure to outdoor or indoor air pollution; a sample of the study population—the controls—is selected and similarly classified according to exposure. An estimate of the relative risk can then be calculated from these data. However, the validity of that estimate depends on both the cases and the controls being selected independent of their exposure.

Cohort and case–control studies of lung cancer are usually retrospective, i.e., lung cancers have already occurred when the study is conducted. Therefore, a strategy is needed for estimating air pollution exposure using historical information. Investigators have generally linked available air pollution monitoring data with residential histories to provide estimates of long-term exposure to air pollution. The exposure of an individual to carcinogens may occur in multiple microenvironments, and therefore may be difficult to characterize

for the purpose of epidemiologic analysis. For example, early lung cancer studies often defined exposure to outdoor air pollution in terms of urban and rural location of residence. More recent investigations have used crude indicators of cumulative exposure to air pollution such as duration of residence in an area characterized by a particular level of pollution. The level is usually derived from routinely collected air monitoring data from one, or at most several, stationary monitoring sites. Although these approaches may identify most truly exposed subjects, they tend to classify some truly unexposed subjects as exposed.

An individual's exposure may also change over time due to, for example, trends in air pollution levels or subject mobility. Although lung cancer is a disease of late adulthood, if air pollution plays a causal role, it is possible that exposures to air pollution in earlier periods may be important. Few, if any, current studies of air pollution and lung cancer have assessed the role of time-varying air pollution exposure on lung cancer occurrence.

Misclassification of exposure can spuriously elevate or diminish estimates of effects. When misclassification rates are the same for exposed cases and controls and for unexposed cases and controls (i.e., nondifferential misclassification), estimates of effect are in most cases attenuated (*40*). When the risk of lung cancer increases directly and monotonically with exposure (sometimes referred to as a dose response), nondifferential misclassification of exposure can obscure this pattern (*41,42*). Most studies attempt to collect data on other lung cancer risk factors such as cigarette smoking, which could confound the air pollution relative risks. Errors in the measurement of potential confounders can have more serious consequences, producing bias in either a positive or negative direction even if air pollution exposures are estimated with relatively little error (*43*). Misclassification of exposure and potential effect modifiers can also create bias and imprecision in estimates of interaction (*44*).

Most published cohort and case–control studies found relative increases of lung cancer risks after adjustment for age, smoking, and occupational exposure similar to those observed in the urban–rural and ecologic studies (Table 2). Dockery and colleagues (*45*) reported the results of a cohort study of 8,111 adults living in six U.S. cities. Cohort members were followed for between 14 and 16 years and their mortality was ascertained through 1989. Lung cancer relative risks were estimated with respect to average levels in each city for various components of air pollution, including total and fine particulate mass, ozone, and sulfate particles. After adjustment for differences in age, sex, cigarette smoking, obesity, and education among cohort members, researchers observed a 37% excess lung cancer risk for a difference in fine particulate mass equal to that of the most polluted versus the least polluted city. However, the exposure of cohort members to fine particulate air pollution (estimated as the average level of fine particulate mass over the entire risk period) was assumed to have been constant throughout their lives, and exposures to other risk factors (such as cigarette smoking) were assumed to have been stable over the approximately 16-year period of follow-up.

In addition to the Six-Cities study (*45*) two other U.S. prospective cohort studies observed increased relative risks of lung cancer associated with exposure to air pollution. Pope and colleagues (*46*) linked ambient air pollution data from 151 U.S. metropolitan areas with risk factor data for 552,138 adults enrolled in the American Cancer Society Cancer Prevention Study II (CPS-II), and monitored for vital status from 1982 to 1989. Using multivariable regression, the investigators controlled for individual differences in age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education, body mass index, and alcohol use. Lung cancer mortality was associated with air pollution when sulfate particulate was used as the index of air pollution exposure but not when fine particle mass (available for only 50 cities and approximately half the study population) was used, as in the Six-Cities study (*45*). This discrepancy did not appear to be due to differences in air monitoring data across the 151 metropolitan areas and remains unexplained.

The Adventist Health Study on Smog reported by Beeson and colleagues (*47*) followed a cohort of Seventh Day Adventists, resident in southern California, whose extremely low prevalence of smoking and uniform (and relatively healthy) dietary patterns reduce the potential for confounding by these factors. Lifetime exposure to a range of air pollutants was estimated for each study subject, using ambient air quality measurements collected by the U.S. EPA and the state of California, residence histories, and questionnaires. Both PM_{10} and ozone were associated with lung cancer (Table 2), but the 5-fold increase in lung cancer rates associated with cumulative exposure to PM_{10} is not consistent with the body of current research and is difficult to explain even in a population with relatively few

Table 2. Epidemiologic studies of outdoor air pollution and lung cancer.

Study	Locale	Exposure classification	Rate ratio (95% CI)
Ecologic			
Henderson (*77*)	Los Angeles, CA	Polycyclic aromatic hydrocarbon levels by geographic area (TSP weekly mean 96–116 μg/m^3)	1.3
Buffler (*78*)	Houston, TX	TSP levels by census tract (RR evaluated at 16.12 μg/m^3)	1.9
Archer (*37*)	Utah	Mean levels of TSP by county (Mean TSP in high air pollution area 85 μg/m^3)	1.6
Case–control			
Pike (*81*)	Los Angeles	Residence in high pollution (benzo[*a*]pyrene) area (TSP weekly mean 96–116 μg/m^3)	1.3[a] (NA)
Vena (*82*)	Buffalo, NY	> 50 years residence in high TSP areas (80–200 μg/m^3)	1.7[a] (1.0–2.9)
Jedrychowski (*83*)	Cracow, Poland	Residence in high TSP (> 150 μg/m^3) and SO_2 (> 104 μg/m^3) areas	1.5[a] (1.1–2.0)
Katsouyanni (*84*)	Athens, Greece	Lifelong residence in high pollution areas (soot levels as high as 400 μg/m^3)	1.1[a] (NA)
Barbone (*48*)	Trieste, Italy	Residence in areas with high levels of particle deposition (> 0.298 g/m^2/day)	1.4[a] (1.1–1.8)
Nyberg et al. (*49*)	Stockholm, Sweden	Long-term (≥ 30 years) residential exposure to traffic-related NO_2	1.3[a] (0.9–1.9)
Cohort			
Beeson (*47*)	California	RR evaluated at mean PM_{10} IQR 24 μg/m^3 (males)	5.2[a] (1.9–13.9)
		RR evaluated at 8-hr mean O_3 IQR 100 ppb (males)	1.7[a] (0.7–3.8)
Dockery (*45*)	6 U.S. cities	Residence in high fine particulate pollution areas (RR evaluated at $PM_{2.5}$ = 18.6 μg/m^3)	1.4[a] (0.8–2.3)
Pope (*46*)	151 U.S. cities	Residence in high sulfate particulate pollution areas (RR evaluated at sulfate = 19.9 μg/m^3)	1.4[a] (1.1–1.7)
		Residence in high fine particulate pollution areas (RR evaluated at $PM_{2.5}$ = 24.4 μg/m^3)	1.0[a] (0.8–1.3)

IQR, interquartile range. [a]Denotes studies that controlled for cigarette smoking. Table modified from Samet and Cohen (*5*).

other risk factors. Unfortunately, the authors do not present the actual incidence rates that might have permitted this issue to be evaluated directly.

Barbone et al. (*48*) conducted a case–control study of lung cancer mortality from 1979 to 1986 and exposure to ambient air pollution in Trieste, Italy. Exposures for 755 individuals who died of lung cancer and 755 controls who died from other causes were estimated as the average level of particle deposition ($g/m^2/day$) for their neighborhood of residence between 1972 and 1979. After controlling for the effects of age, smoking, and occupation, a 40% increase in the lung cancer mortality rate (RR = 1.4; 95% CI 1.1, 1.8) was observed among those who resided in neighborhoods with the highest levels of particle deposition (> 0.298 $g/m^2/day$). Case–control studies based only on deceased individuals present certain well-known interpretative problems. Here, 55% of the controls had died from cardiovascular disease, which itself has been associated with particulate air pollution (*45*). If the association with cardiovascular mortality is valid, and the only feature that distinguished residential areas was the level of air pollution, then the observed relative risk would be an underestimate of the true relative risk. If, however, other features of residential area (e.g., social class) are also associated with cardiovascular mortality, then the air pollution relative risk in this study may be an overestimate.

Nyberg and colleagues (*49*) recently completed a case–control study of air pollution and lung cancer in the general population of Stockholm, Sweden (the LUCAS study) that attempted to identify the sources of urban air pollution most strongly associated with lung cancer. The study included all lung cancers (n = 1,042) that occurred among male residents of Stockholm, 40–75 years of age, from 1985 to 1990. Historical measurements of SO_2 and NO_2/NO_x were combined with residence histories to provide estimates of long-term exposure to air pollution from fuel combustion from residential heating and traffic, respectively. Exposure for 30 years to NO_2 in the highest decile was associated with a relative risk of 1.3 (95% CI 0.9, 1.9) after adjustment for cigarette smoking, occupational exposure, and radon exposure, and the relative risk in this decile after the 21- to 30-year induction time was 1.6 (95% CI 1.1, 2.4). No positive associations were reported for SO_2.

Studies of the Relative Frequency of Biologic Air Pollution Exposure and Genetic Damage

Exposure biomarkers—that is, indicators of exposure or dose measured in biologic material—offer a new approach to quantifying the lung cancer risk associated with air pollution. Potential biomarkers for lung cancer risk include actual levels of the putative carcinogen in biologic materials, DNA adducts of potential carcinogens or metabolites, and antibodies against such adducts (*50*). Biomarkers of exposure to respiratory carcinogens provide an intermediate outcome for investigation that may prove valid surrogates for risk. Levels of adducts, for example, may prove to be predictors of risk and may bridge from animal models and *in vitro* assays to human risk. These methods may enable epidemiologists to reduce bias from misclassification of exposure, but these methods are in their infancy and will require careful study and more extensive application before their true utility is known.

Studies of biomarkers of air pollution exposure and intermediate effects related to carcinogenicity have focused largely on a single group of carcinogens present in urban air: the PAHs, of which benzo[*a*]pyrene is the prototype. The concentration of benzo[*a*]pyrene can be measured in the air and a number of studies have examined the association between exposure to benzo[*a*]pyrene and other PAHs and marker levels, including PAH–DNA adducts, sister chromatid exchange, chromosome aberrations, and oncogene proteins; associations generally have been positive. For the most part, exposure to PAHs has been studied in occupationally exposed workers, including foundry workers and traffic police, but it also has been studied in residents of highly polluted urban environments, largely in Eastern Europe.

Perera and colleagues (*51,52*) investigated biomarkers in residents of a highly industrialized region of Silesia in Poland. Levels of benzo[*a*]pyrene were markedly elevated due to industrial activity and coal combustion for residential heating. Airborne particulate matter collected in this region was subjected to assays for mutagenicity and found to have genotoxic activity in a variety of short-term tests. Compared with controls from a less polluted region, persons residing in Silesia had significant increases in carcinogen–DNA adducts, sister chromatid exchange, and chromosomal aberrations. They also showed a doubling of the frequency of *ras* oncogene overexpression. These results indicate the potential to estimate lung cancer risk by combining information on concentrations of carcinogens in outdoor air with levels of adducts in exposed persons; the levels of biomarkers could then be used to predict cancer risks once the biomarkers are validated (*53*). Workers in certain occupations, including foundries or jobs involving heavy vehicle exhaust exposure, have also been investigated for levels of biomarkers of exposure to PAHs. In a study of foundry workers in Finland, levels of DNA adducts with PAHs were associated with workplace exposure (*54,55*).

Studies have also been conducted of biomarkers in traffic police workers and bus drivers. In a study of traffic police workers in Italy, levels of micronuclei in peripheral blood lymphocytes were not increased in the police workers in comparison with controls (*56*). Urinary excretion of 1-hydroxypyrene, however, did appear to be a useful biomarker for exposure to air pollution by PAHs. In contrast, bus drivers working in central Copenhagen, Denmark, had higher levels of PAH–DNA adducts in comparison with controls (*57*).

Air Pollution and Lung Cancer in Less-Developed Countries

Mounting evidence indicates that populations in less-developed countries may have exposure to indoor and outdoor environments that rival or even dramatically exceed those found in developed Western countries. Indoor air pollution from coal combustion and cooking fumes has been linked to increased lung cancer risk in homes in China and Hong Kong (*58*). Rising pollution of outdoor air in the mega-cities of the developing world may also pose a risk for lung cancer.

Within the less-developed countries, the highest exposures, particularly among women, have been to indoor air pollution from the combustion of coal and biomass fuels for cooking and heating (*59*). For example, typical concentrations of coal smoke in rural homes in China exceeded 500 $\mu g/m^3$ and frequently exceeded 1 mg/m^3. Smith and Liu (*58*) recently reviewed the epidemiologic literature on indoor air pollution and lung cancer in the developing countries and found consistent evidence of increased rates of lung cancer associated with indoor cooking and heating with coal in studies done largely in China. A much smaller group of studies revealed no consistent association of lung cancer with indoor use of biomass fuels.

Mounting levels of urban air pollution, from local stationary and, increasingly, mobile sources (*60*) are recognized as an important environmental problem by international public health and economic agencies. In the cities of the poorest countries, the Global Environmental Monitoring System of the World Health Organization observed average ambient concentrations of total suspended particles of 300 mg/m^3 (*61*), although levels in locales where coal is used for fuel, such as poor communities in South Africa, may exceed 1 g/m^3. Although there are currently few relevant investigations, a case–control study in Shenyang, China, observed a 2-fold increase in lung cancer risk after adjustment for age, education, and smoking among residents in smoky areas of

the city and a 50% increase among those in somewhat or slightly smoky areas (*62*).

Estimating the Impact of Air Pollution on Lung Cancer Rates

Estimation of the magnitude of the contribution of air pollution to lung cancer occurrence at contemporary levels of air pollution poses a major challenge. Samet (*63*) recently reviewed the issue of risk assessment of air pollution exposure. Historically, estimates of the population attributable risk of lung cancer due to outdoor air pollution have used diverse approaches and produced variable estimates. Basing their estimate on past and then current estimates of benzo[*a*]pyrene in urban air and extrapolation from occupational studies of PAH-exposed workers, Doll and Peto (*27*) estimated that less than 1% of future lung cancer would be due to air pollution from the burning of fossil fuels. They did note, however, that perhaps 10% of then-current lung cancer in large cities might have been due to air pollution. In 1990, the U.S. EPA (*64*) estimated that 0.2% of all cancer, and probably less then 1% of lung cancer, could be attributed to air pollution. This estimate was obtained by applying the unit risks for more than 20 known or suspected human carcinogens found in outdoor air to estimates of the ambient concentrations and numbers of persons potentially exposed. The unit risks were derived either from animal experiments or extrapolation from studies of workers exposed to higher concentrations. One group based their estimates on direct observation of populations exposed to ambient levels of air pollution. Karch and Schneiderman (*65*), using data from the American Cancer Society (CPS-I) study and U.S. Census data, estimated that the urban factor accounted for 12% of lung cancer in 1980. They predicted that 1980 levels of TSP (approximately 60 $\mu g/m^3$) would be associated with a lung cancer rate ratio of 1.32, slightly less than the 47% increase observed at an approximate 55.8 $\mu g/m^3$ level of TSP in the Six Cities study (*66*).

Each attributable risk estimate cited above is subject to considerable uncertainty because of a lack of knowledge about both the relative magnitude of the effect and the proportion of the population exposed, but there seems to be no compelling argument to prefer estimates based on extrapolation from animal experiments or occupational studies to direct epidemiologic observation of the general populations at risk if valid and reasonably precise epidemiologic results are available.

Conclusions and Research Needs

The repeated associations between lung cancer occurrence and air pollution, chiefly from the combustion of fossil fuels, observed in studies of varied design and in diverse settings, suggest that such exposures may cause small relative increases in lung cancer rates. This interpretation is consistent with studies of other types of exposure to combustion-source pollution such as occupational exposures and exposures to environmental tobacco smoke. Errors in the measurement of air pollution exposure and in the measurement of other risk factors including cigarette smoking continue to limit our ability to quantify the magnitude of the excess lung cancer risks associated with air pollution.

Relative to cigarette smoking, the excess lung cancer risk associated with ambient air pollution is small. Nonetheless, given the ubiquity of combustion-source ambient air pollution exposure, the contribution of this exposure across a population may be of public health importance even if exposure to ambient air pollution causes but a small proportion of annual lung cancer mortality (which currently totals approximately 150,000 deaths annually in the United States).

Direct epidemiologic observation of exposed populations may yet provide better information for evaluating the magnitude of outdoor air pollution-related excess lung cancer, but because the expected relative effect of air pollution is likely to be weak in many settings, new studies that could better guide policies for protection of public health will face considerable challenges.

In general, large-scale epidemiologic studies of air pollution and lung cancer will be needed if we are to obtain sufficiently informative data, but it is not obvious that such studies are feasible. Assessing their feasibility is a key research need.

Large numbers of cases will be necessary to measure accurately and precisely the small relative excesses that have been observed and to measure the joint effects of air pollution and other factors such as occupation and smoking. The example of residential radon (Rn) provides a useful analogy. Lubin et al. (*67*) considered the feasibility of conducting valid and precise case–control studies of lung cancer and residential exposure to Rn and its decay products given the expectation of small relative effects, errors in the measurement of exposure, and other sources of bias such as subject mobility. All these conditions apply in the case of ambient air pollution, except that the problems posed by measurement error in the air pollution case are, if anything, more serious. Lubin and colleagues concluded that the required study size might well be infeasible and recommended pooling the data from existing studies with the largest number of cases and most precise exposure estimates. It is not at all clear, however, that this solution could be applied to studies of a single ambient air pollutant if only because, in contrast to Rn studies in which exposure assessment methods to a single pollutant are relatively uniform, investigators used a wide variety of indices to characterize the exposure of study subjects to the complex mixture of ambient air pollution.

Without improved epidemiologic methods, however, even large studies may fail to inform. Current development of biologic markers of exposure to and molecular effects of PAHs represents one approach to improving epidemiologic methods. Markers of genetic susceptibility are also needed. In addition and of equal importance, methods for the retrospective estimation of long-term exposure to air pollutants should be developed and tested so that large case–control and retrospective cohort studies can be feasibly conducted. Recent approaches to developing such estimates have combined time–activity information, including long-term residential histories, with data from national aerometric databases such as the Aeromatic Information Retrieval System (AIRS) database maintained by the U.S. EPA (*49,68,69*). Airport visibility data, routinely collected for several decades across the United States, may also provide a historical record of aerometric data that could be used to estimate past levels of outdoor particulate air pollution (*84*). This effort should include development of methods to characterize, quantify, and adjust for exposure measurement error. For lung cancer, urban and relatively unpolluted areas with established population-based tumor registries might be targeted.

Although most case–control and cohort studies have tried to address confounding due to cigarette smoking and occupation, virtually none have addressed possible bias due to the measurement errors in exposure and covariates. Such bias, even if it is nondifferential, can produce either spuriously high or low estimates of the lung cancer rate ratio in multivariable data (*40*). The problem is that few if any studies have collected the data necessary to quantify this bias, or often even to determine its likely direction. These problems are particularly serious when the relative effects are small. Future studies should develop methods and collect data that can be used to quantify exposure measurement error and compute adjusted effect estimates. Some specific areas for future research should include:

Identification of the pollutants and pollution sources associated with increased occurrence of lung cancer. Studies in single locales where levels of individual pollutants are highly correlated will generally be unable to estimate the contributions of specific pollutants or sources, although arguably this may be possible in certain situations such as the Swedish case–control study discussed previously (*49*). New designs and statistical methods for air pollution studies may provide

additional insights. Navidi et al. (*70*) and Prentice and Sheppard (*71*) have described hybrid studies that combine ecologic-level contrasts of air pollution effects between cities with individual-level data on covariates, combining the strengths of both ecologic and individual-level studies. Studies using these designs could contrast the effect on lung cancer of exposure to the pollutant mixtures of different cities while effectively controlling confounding by cigarette smoking, diet, or other factors, and adjusting for exposure measurement error. Such a study might be carried out in the United States using the combined resources of the Surveillance, Epidemiology and End Results (SEER) cancer registry or other population-based cancer registries, and the AIRS and other air pollution databases maintained by the U.S. EPA. If the air pollution mixtures in various U.S. population centers could be characterized both in terms of physical and chemical constituents and sources of major constituents, then it might be possible to retrospectively estimate long-term pollutant- and source-specific exposures of study subjects.

Studies of occupational cohorts have historically provided important information about the carcinogenicity of specific pollutants such as diesel exhaust, to which the general population is exposed, as discussed previously. Although epidemiologists have, for reasons of study power, traditionally sought out occupational groups exposed to levels of pollution well in excess of ambient levels, there may be a benefit to focusing future research on occupational groups who are exposed to levels of pollution more comparable (in terms of intensity) to those of the general population. With regard to diesel exhaust, for example, studies of truck or taxi drivers, may combine the methodologic strengths of studies based in an occupational population with the generalizability of near ambient-level exposures.

Investigation of the etiologic mechanisms that might underlie air pollution's role in lung cancer occurrence, including its role in the association of lung cancer with preexisting respiratory disease. The risk of lung cancer is increased among people with preexisting lung disease (e.g., chronic obstructive pulmonary disease and asthma) and among those who have exhibited accelerated rates of decline in pulmonary function (*72*). Long-term exposure to air pollution has also been associated with low levels of lung function and chronic respiratory symptoms in several cross-sectional and longitudinal studies of children (*73–77*). These reported associations suggest mechanisms other than, or in addition to, the direct initiation or promotion of lung tumors, by which prolonged exposure to air pollution could increase lung cancer risk. For example, chronic and/or episodic inflammatory insults such as those that characterize asthma have been hypothesized to play a role in lung carcinogenesis.

Ideally, longitudinal observation of large populations over decades would be required to determine the possible role of long-term exposure to air pollution in the pathogenesis of chronic respiratory disease and the subsequent development of lung cancer. If the current high level of interest in the effects of long-term exposure to particulate air pollution on chronic disease incidence and mortality results in either new cohort studies or the retro-fitting of existing cohorts with air pollution data, such longitudinal observations may be possible.

Measurement of the interaction of ambient air pollution with other known or suspected causes of lung cancer, i.e., cigarette smoking, occupation, and diet. The effect of air pollution on lung cancer occurrence may depend, perhaps critically, on other factors, such as cigarette smoking, genetic predisposition, diet, occupational exposures, and social class, to cause lung cancer. Some reviewers have noted a greater-than-additive relationship between air pollution and cigarette smoking that would imply synergism (*26,65*). Estimates of the magnitude of the effect of joint exposure to ambient air pollution and cigarette smoking have been reported or can be derived from several studies (*65*), and although these results appear to suggest a greater-than-additive relation between cigarette smoking and ambient air pollution (anywhere from 20 to 45% of cases attributable to joint exposure), they are subject to error from inaccurate measurement of both air pollution exposure and cigarette smoking, and to substantial imprecision due to small numbers of lung cancer cases among nonsmokers.

Although the combined effects of ambient air pollution and smoking have not been well characterized, the combined effects of smoking with air pollution merits particular consideration because of the strength of smoking as a cause of lung cancer and the continued high, and in some cases growing, prevalence of smoking in many parts of the world. However, as illustrated by the example of residential Rn noted previously, prohibitively large studies, and unachievably accurate measurement of both air pollution and cigarette smoking may be required to provide valid estimates of combined effects (*76*).

Studies of the contribution of ambient air pollution to lung cancer occurrence in less-developed countries currently undergoing rapid urbanization. Current knowledge about ambient air pollution and lung cancer is based largely on the experience of populations of Western industrialized nations. However, industrial and infrastructure development in poorer countries has led to increases in urban air pollution that may contribute to increased occurrence of lung cancer.

As a greater proportion of the world's population moves from rural communities to the rapidly expanding and highly polluted cities of Asia and the Southern Hemisphere, there is a need to address the large gap in epidemiologic research on air pollution and lung cancer in the developing world.

These studies will present even greater challenges than those in the industrialized West. In addition to the generic problem of estimating long-term exposure to air pollution, the ambient air pollution mixture in urban centers in the developing countries is changing, due in part to the increase in automobile traffic. Characterizing these changes as they occur over time, including choosing and measuring indicator pollutants for different pollution sources, requires careful planning. In addition, the current increases in cigarette smoking in the developing world (*61*), and their thoroughly predictable consequences, will complicate interpretation of future studies of air pollution and lung cancer.

References and Notes

1. Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. Br Med J 2:740–748 (1950).
2. White C. Research on smoking and lung cancer: a landmark in the history of chronic disease epidemiology. Yale J Biol Med 63:29–46 (1990).
3. Tomatis L, ed. Air Pollution and Human Cancer. In: European School of Oncology Monographs. Berlin:Springer-Verlag, 1990.
4. Cohen AJ, Pope CA III, Speizer FE. Ambient air pollution as a risk factor for lung cancer. Salud Publica Mex 39(3):349–355 (1997).
5. Samet JM, Cohen AJ. Air pollution and lung cancer. In: Air Pollution and Health (Holgate S, Koren H, Maynard R, Samet JM, eds). London:Academic Press, 1999;841–864.
6. Council for Environmental Quality. Eleventh Annual Report of the Council on Environmental Quality. Washington, DC:U.S. Government Printing Office, 1980.
7. Daisey JM, Lioy PJ, Daisy JM, eds. Toxic Air Pollution—A Comprehensive Study of the Non-Criteria Air Pollutants. Chemical Composition of Inhalable Particulate Matter: Seasonal and Inter-Site Comparisons. Chelsea, MI:Lewis Publishers,1988.
8. U.S. EPA. National Air Quality and Emissions Trends Report, 1995. EPA 454/R-96-005. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1996.
9. Cass GR, Conklin MH, Shah JJ, Huntzicker JJ, Macias ES. Elemental carbon concentrations: estimation of an historical data base. Atmos Environ 18:153–162 (1984).
10. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7: Overall Evaluations of Carcinogenicity, an Updating of IARC Monographs. Lyon:Internatonal Agency for Research on Cancer, 1987.
11. Greenberg A. Analyses of polycyclic aromatic hydrocarbons. In: Toxic Air Pollution: A Comprehensive Study of Non-Criteria Air Pollutants (Daisey JM, Lioy MJY, eds). Chelsea, MI:Lewis Publishers, 1987;93–118.
12. Natusch DF. Potentially carcinogenic species emitted to the atmosphere by fossil-fueled power plants. Environ Health Perspect 22:79–90 (1978).
13. Winer AM, Busby WF Jr. Atmospheric transport and transformation of diesel emissions. In: Health Effects of Diesel Engine Emissions: Characterization and Critical Analysis. Cambridge, MA:The Health Effects Institute, 1995.
14. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Cause Control 8:444–472 (1997).
15. Doll R, Vessey MP, Beasley RWR, Buckley AR, Fear EC, Fisher REW, Gammon EJ, Gunn W, Hughes GO, Lee K, et al. Mortality

of gas workers. Final report of a prospective study. Br J Ind Med 29:394–406 (1972).
16. Redmond CK. Cancer mortality among coke oven workers. Environ Health Perspect 52:67–73 (1983).
17. IARC. Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Polynuclear Aromatic Compounds. Vol 34, Pt 3. Lyon:International Agency for Research on Cancer, 1984.
18. Koutrakis P, Sioutas C. Physico-chemical properties and measurement of ambient particles. In: Particles in Our Air: Concentrations in Health Effects (Spengler JD, Wilson R, eds). Cambridge, MA:Harvard University Press, 1996;15–40.
19. Cohen AJ, Nikula K. The health effects of diesel exhaust: laboratory and epidemiologic studies. In: Samet JM, Cohen AJ. Air Pollution and Lung Cancer. In: Air Pollution and Health, Vol 32 (Holgate S, Koren H, Maynard R, Samet JM, eds). London: Academic Press, 1999;707–748.
20. IARC. Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 54. Lyon:International Agency for Research on Cancer, 1992.
21. Cass GR, Gray HA. Regional emissions and atmospheric concentrations of diesel engine particulate matter: Los Angeles as a case study. In: Health Effects of Diesel Engine Emissions: Characterization and Critical Analysis. Cambridge, MA:The Health Effects Institute, 1995.
22. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 46: Diesel and Gasoline Engine Exhausts and Some Nitroarenes. Lyon:International Agency for Research on Cancer, 1989.
23. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am J Public Health 89:1009–1017 (1999).
24. Health Effects Institute. Research Priorities for Mobile Air Toxics. HEI Communication No 2. Cambridge, MA:Health Effects Institute, 1993.
25. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 62: Wood Dust and Formaldehyde. Lyon:International Agency for Research on Cancer, 1995.
26. Speizer FE, Samet JM. Air pollution and lung cancer. In: Epidemiology of Lung Cancer (Samet JM, ed). New York:Marcel Dekker, 1994;131–146.
27. Doll R, Peto R. The Causes of Cancer. Oxford:Oxford University Press, 1981.
28. Dean G, Lee PN, Todd GF, Wicken AJ. Report on a Second Retrospective Mortality Study in Northeast England: Parts 1 and 2. London:Tobacco Research Council, 1978.
29. International Agency for Research on Cancer (IARC). Cancer in Five Continents. Vol VII. Lyons, France:International Agency for Research on Cancer, 1997.
30. Kadafar K, Freedman LS, Goodall CR, Tukey JW. Urbanicity-related trends in lung cancer mortality in US counties: white females and white males, 1970-1987. Int J Epidemiol 25(5):918–932 (1996).
31. Hannigan MP, Cass GR, Penman BW, Crespi CR, Lafleur AL, Busby WF Jr, Thilly WG. Human cell mutagens in Los Angeles air. Environ Sci Technology 31(2):438–447 (1997).
32. Pedersen DU, Durant JL, Penman BW, Crespi CL, Hemond HF, Lafleur AL, Cass GR. Seasonal and spatial variations in human cell mutagenicity of respirable airborne particles in the northeastern United States. Environ Sci Technology 33(24):4407–4415 (1999).
33. Pershagen G, Elinder CG, Bolander AM. Mortality in a region surrounding an arsenic smelting plant. Environ Health Perspect 19:133–137 (1977).
34. WHO. Emissions of Heavy Metal and PAH Compounds from Municipal Solid Waste Incinerators: Control Technology and Health Effects. Report on a WHO meeting, Florence. Copenhagen:World Health Organization, 1988.
35. Kogevinas M, Pearce N, Susser E, Boffetta P, eds. Social Inequalities in Cancer. No 138. Lyon:International Agency for Research on Cancer, 1997.
36. Pershagen G. Air pollution and cancer. In: Complex Mixtures and Cancer Risk (Pershagen G, Vainio H, Sorsa M, McMichael AJ, eds). Lyon:International Agency for Research on Cancer, 1990;240–251.
37. Archer VE. Air pollution and fatal lung disease in three Utah counties. Arch Environ Health 45:325–334 (1990).
38. Elliott P, Shaddick G, Kleinschmidt I, Jolley D, Walls P, Beresford J, Grundy C. Cancer incidence near municipal solid waste incinerators in Great Britain. Br J Cancer 73:702–710 (1996).
39. Greenland S, Robins J. Invited commentary: ecologic studies-biases, misconceptions, and counterexamples. Am J Epidemiol 139(8):747–760 (1994).
40. Hatch M, Thomas D. Measurement issues in environmental epidemiology. Environ Health Perspect 101(suppl 4):49–57 (1993).
41. Birkett NJ. Effect of nondifferential misclassification on estimates of odds ratios with multiple levels of exposure. Am J Epidemiol 136:356–362 (1992).
42. Dosemici M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 132:746–768 (1990).
43. Greenland S. The effect of misclassification in the presence of covariates. Am J Epidemiol 112:564–569 (1980).
44. Garcia-Closas M, Rothman N, Lubin J. Misclassification in case-control studies of gene-environment interactions: assessment of bias and sample size. Cancer Epidemiol Biomarkers Prev 8:1043–1050 (1999).
45. Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329(24): 1753–1759 (1993).
46. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151(3):669–674 (1995).
47. Beeson WL, Abbey DE, Knutsen SF. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Environ Health Perspect 106(12):813–823 (1998).
48. Barbone F, Bovenzi M, Cavalleri F, Stanta G. Air pollution and lung cancer in Trieste, Italy. Am J Epidemiol 141(12):1161–1169 (1995).
49. Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R, Pershagen G. Urban air pollution and lung cancer in Stockholm. Epidemiology (in press).
50. Schulte PA, Perera FP, eds. Molecular Epidemiology: Principles and Practices. New York:Academic Press, 1993.
51. Motykiewicz G, Perera FP, Santella RM, Hemminki K, Seemayer NH, Chorazy M. Assessment of cancer hazard from environmental pollution in Silesia. Toxicol Lett 88(1–3):169–73 (1996).
52. Perera FP, Hemminki K, Gryzbowska E, Motykiewicz G, Michalska J, Santella RM, Young TL, Dickey C, Brandt-Rauf P, DeVivo I, et al. Molecular and genetic damage in humans from environmental pollution in Poland. Nature 360(6401):256–258 (1992).
53. Perera FP, Mooney LA, Dickey CP, Santella RM, Bell D, Blaner W, Tang D, Whyatt RM. Molecular epidemiology in environmental carcinogenesis. Environ Health Perspect 104(suppl 3):441–443 (1996).
54. Hemminki K, Dickey C, Karlsson S, Bell D, Hsu Y, Tsai WY, Mooney LA, Savela K, Perera FP. Aromatic DNA adducts in foundry workers in relation to exposure, life style and CYP1A1 and glutathione transferase M1 genotype. Carcinogenesis 18(2):345–350 (1997).
55. Perera FP, Dickey C, Santella R, O'Neill JP, Albertini RJ, Ottman R, Tsai WY, Mooney LA, Savela K, Hemminki K. Carcinogen-DNA adducts and gene mutation in foundry workers with low-level exposure to polycyclic aromatic hydrocarbons. Carcinogenesis 15(12):2905–2910 (1994).
56. Merlo F, Andreassen A, Weston A, Pan CF, Haugen A, Valerio F, Reggiardo G, Fontana V, Garte S, Puntoni R, et al. Urinary excretion of 1-hydroxypyrene as a marker for exposure to urban air levels of polycyclic aromatic hydrocarbons. Cancer Epidemiol Biomarkers Prev 7(2):147–155 (1998).
57. Nielsen PS, de Pater N, Okkels H, Autrup H. Environmental air pollution and DNA adducts in Copenhaen bus drivers—effect of GSTM1 and NAT2 genotypes on adduct levels. Carcinogenesis 17(5):1021–1027 (1996).
58. Smith KR, Liu Y. Indoor air pollution in developing countries. In: Epidemiology of Lung Cancer (Samet JM, ed). New York:Marcel Dekker, 1996;151–179.
59. Smith KR. Fuel combustion, air pollution exposure, and health: the situation in developing countries. Ann Rev Energy Environ 18:529–566 (1993).
60. Kenworthy JR. Automobile dependence in Bangkok: an international comparison with implications for planning policies and air pollution. In: Health at the Crossroads: Transport Policy and Urban Health (Fletcher T, McMichael AJ, eds). New York:John Wiley and Sons, 1997;215–234.
61. WHO. Global Estimates for Health Situation Assessment and Projections. HST/90.2. Geneva:World Health Organization, 1990.
62. Xu ZY, Blot WJ, Xiao HP, Wu A, Feng WP, Stone BJ, Jie S, Ershow AG, Henderson BE, Fraumeni JF. Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. JNCI 8:1800–1806 (1989).
63. Samet JM. Risk assessment and air pollution. In: Air Pollution and Health (Holgate S, Koren H, Maynard R, Samet JM, eds). London:Academic Press, 1999;881–898.
64. U.S. EPA. Cancer Risk from Outdoor Exposure to Air Toxics. Vol 1. Final Report. EPA-450/1-90-004a. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1990.
65. Karch NJ, Schneiderman MA. Explaining the Urban Factor in Lung Cancer Mortality. A Report of the Natural Resources Defense Council. Washington, DC:Clement Associates, Inc., (1981).
66. Dockery D. Personal communication.
67. Lubin JH, Samet JM, Weinberg C. Design issues in epidemiologic studies of indoor exposure to Rn and risk of lung cancer. Health Physics 59(6):807–817 (1990).
68. Künzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen-results of a pilot study. Environ Res 72:8–23 (1997).
69. Aerometric Information Retrieval Service Database. Washington, DC:U.S. Environmental Protection Agency. Available: *http://www.epa.gov/airs/airs.html* [cited 1999].
70. Navidi W, Thomas D, Stram D, Peters J. Design and Analysis of Multigroup Analytic Studies with Applications to the Study of Air Pollution. Technical Report No 49. Los Angeles, CA:University of Southern California,1993.
71. Prentice RL, Sheppard L. Aggregate data studies of disease risk factors. Biometrika 82:113–125 (1995).
72. Tockman MS. Other host factors and lung cancer susceptibility. In: Epidemiology of Lung Cancer (Samet JM, ed). New York:Marcel Dekker, 1994;397–412.
73. Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, Speizer FE. Health effects of acid aerosols on North American children: pulmonary function. Environ Health Perspect 104(5):506–514 (1996).
74. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H Jr, et al. A study of twelve Southern California communities with differing levels and types of air pollution. I: Prevalence of respiratory morbidity. Am J Respir Crit Care Med 159:760–767 (1999).
75. Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong H Jr, Thomas D. A study of twelve Southern California communities with differing levels and types of air pollution. II: Effects on pulmonary function. Am J Respir Crit Care Med 159:768–775 (1999).
76. Van de Lende R, Kok TJ, Reig RP, Quanjer PH, Schouten JP, Orie G. Decreases in VC and FEV_1 with time: indicators for the effect of smoking and air pollution. Bull Eur Physiopathol Respir 17:775–792 (1981).
77. Detels R, Tashkin DP, Sayre JW, Rokaw SN, Massey FJ, Coulson AH, Wegman DH. The UCLA population studies of CORD. X: A cohort study of changes in respiratory function associated with chronic exposure to SO_x, NO_x, and hydrocarbons. Am J Public Health 81:350–359 (1991).
78. Lubin JH, Gail MH. On power and sample size for studying features of the relative odds of disease. Am J Epidemiol 131(3):552–566 (1990).
79. Henderson BE, Gordon RJ, Menck H, Soohoo J, Martin SP, Pike MC. Lung cancer and air pollution in Southcentral Los Angeles County. Am J Epidemiol 101(6):477–488 (1975).
80. Buffler PA, Cooper SP, Stinnett S, Contant C, Shirts S, Hardy RJ, Agu V, Gehan B, Burau K. Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. Am J Epidemiol 128:683–699 (1988).
81. Pike MC, Jing JS, Rosario IP, Henderson BE, Menck HR. Occupation: "explanation" of an apparent air pollution related localized excess of lung cancer in los angeles county. In: Energy and Health (Breslow N, Whitemore A, eds). Philadelphia:SIAM, 1979;3–16.
82. Vena JE. Air pollution as a risk factor in lung cancer. Am J Epidemiol 116:42–56 (1982).
83. Jedrychowski W, Becher H, Wahhrendorf J, Basa-Cierpialek Z. A case-control study of lung cancer with special reference to the effect of air pollution in Poland. J Epidemiol Commun Health 44:114–120 (1990).
84. Katsouyanni K, Karakatsani A, Messari I, Touloumi G, Hatzakis A, Kalandidi A, Trichopoulos D. Air pollution and cause specific mortality in Athens. J Epidemiol Commun Health 44:321–324 (1990).
85. Ozkaynak H, Schatz A, Thurston G. Relationship between aerosol extinction coefficient derived from airport visual range and alternative measures of airborn particle mass. Air Pollut Control Assoc J 35:1176–1185 (1985).